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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	
MAIL DATE	**DELIVERY MODE**
07/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/606,159	JANJIC ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *1-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/6/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 6, 2007 has been entered.

Election/Restrictions

Claims 1-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 16, 2006.

Claim Rejections - 35 USC § 103

Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gold et al. in view of Tullis and Ferns et al. (all of record).

Claim 7 is directed to a method of improving the pharmacokinetic properties of a PDGF nucleic acid ligand by covalently linking the ligand to either a lipophilic compound

or a non-immunogenic, high molecular weight compound and administering the complex to a patient. Claim 8 is directed to a method of targeting a therapeutic or diagnostic agent to a particular predetermined biological target in a patient by covalently linking the agent to a complex of a PDGF nucleic acid ligand and a lipophilic compound or a non-immunogenic, high molecular weight compound and administering the complex to a patient.

Gold et al. teach a method of identifying nucleic acid ligands by a process of *in vitro* selection and amplification. Targets for nucleic acid ligands include growth factors. Nucleic acid ligands are also referred to as nucleic acid antibodies and Gold et al. teach that nucleic acid ligands can be employed in diagnostics in a manner similar to conventional antibody-based diagnostics. Gold et al. also teach that nucleic acid ligands have therapeutic uses as sequestering agents, drug delivery vehicles and modifiers of hormone action. Gold et al. do not teach conjugation of a nucleic acid ligand to a non-immunogenic, high molecular weight compound or a lipophilic compound.

Tullis teaches nucleic acid conjugates comprising an antisense conjugated to a solubility modifying moiety that may be hydrophobic and imparts amphiphilic character to the final product. At page 7 solubility modifying moieties are taught as including polyethylene glycol as well as lipophilic compounds such as palmitate, distearylglyceride and cholesteryl. Tullis teaches that the conjugates of the invention find use in therapeutics wherein the amphiphilic nature of the conjugate aids in transport

across the cellular membrane and that the conjugates improve other pharmacokinetic properties such as nuclease resistance.

Ferns et al. teach that PDGF is involved in the accumulation of smooth muscle cells that is the main cause of restenosis after angioplasty. Ferns et al. further teach that administration of PDGF antibodies to rats before and after balloon catheter deendothelialization, a model of angioplasty induced restenosis, reduced the amount of smooth muscle cell accumulation observed. Ferns et al. teach that their findings suggest possible approaches for prevention of restenosis following angioplasty.

It would have been obvious to one of ordinary skill in the art at the time of invention to improve the pharmacokinetic properties of a nucleic acid ligand as taught by Gold et al. by conjugating the ligand to a solubility modifying moiety such as PEG or cholesterol as taught by Tullis. It would have been further obvious to one of ordinary skill to make nucleic acid ligands that are targeted to PDGF. Tullis provides a motivation to make conjugates of nucleic acids and solubility modifying moieties, teaching that such conjugates increase pharmacokinetic properties such as cellular uptake and nuclease resistance. It would have further been obvious to use a nucleic acid ligand complex to deliver a therapeutic or diagnostic agent because Gold et al. explicitly suggest drug delivery vehicles are one of the utilities of nucleic acid ligands. Ferns et al. provide a motivation to target PDGF, teaching that PDGF is involved in the accumulation of smooth muscle cells that is the main cause of restenosis and that inhibition of PDGF reduces restenosis. One of ordinary skill in the art would have had a reasonable expectation of success in producing a nucleic acid ligand to PDGF because

Gold et al. teach a method of isolating nucleic acid ligands to any target molecule and state that growth factors are a desired target. One of ordinary skill in the art would have had a reasonable expectation of success in making a conjugate of solubility modifying moiety and a nucleic acid ligand because Tullis teaches that such oligonucleotide conjugates are made using routine synthesis methods.

Thus, the invention of claims 7 and 8 would have been obvious, as a whole, at the time of invention.

Response to arguments

Applicants traverse the 103 rejection by arguing there is no reasonable expectation of success in combining the references. To support this argument, applicants note that Tullis teaches nucleic acid conjugates for affecting intracellular events, citing page 41,

> "the amphiphilic nature of the product [nucleic acid conjugate] aids in the transport of the conjugate across the cellular membrane, and can provide additional advantages, such as increasing aqueous or liquid solubility of nucleic acid derivatives, e.g., use of an amphiphilic group to enhance water solubility of long chain methyl phosponates and stabilizing normal nucleic acids to exonuclease digestion."

Based on this sentence applicants conclude Tullis does not teach or suggest the plasma half life of a nucleic acid molecule can be extended by conjugating to a molecule such as PEG and conclude the teachings of this reference are limited to conjugates that pass the cellular membrane, i.e. those that act on intracellular targets. Applicants argue that one advantage of the instant invention, however, is increase of the plasma half life of PDGF nucleic acid ligands and further argue the nucleic acid

ligands of the invention do not have to enter the cell because PDGF is a growth factor, which is an extracellular target.

This argument is not persuasive because the teachings of Tullis are not limited to conjugates that act intracellularly; the sentence quoted by applicants refers not only to cellular uptake, but also to stability of the conjugate to exonuclease digestion. The claims recite the improvement of pharmacokinetic properties and exonuclease resistance is one such property. Since exonucleases are present in plasma this property is important for agents that function extracellularly as well as intracellularly. Applicants' arguments are also not persuasive because while PDGF may ultimately exist extracellularly it is made within cells and exists intracellularly as well. The instant claims are not limited to extracellular embodiments.

Applicants further traverse the 103 rejection by clarifying that previous remarks made in response to a now-withdrawn written description rejection regarding the highly developed state of the art regarding conjugation of lipophilic compounds and/or high molecular weight compounds to therapeutically active compounds were made with respect to the lipophilic compounds/high molecular weight moieties only and were not directed to the state of the art with regard to nucleic acid ligands. This clarification is acknowledged but does not change the examiner's position because this was precisely the interpretation given to the remarks. These remarks note only that there is a reasonable expectation of success in making a conjugate comprising a molecule such as PEG. That is, that synthetic procedures to produce conjugates comprising high molecular weight compounds are well-known to those in the art.

It is noted that because applicants state "such maturity does not per se suggest that it can be predicted with reasonable expectation of success that combinations of the same with nucleic acid ligands would lead to successful therapeutic compounds", applicants appear to believe a prediction of therapeutic effect is required for a reasonable expectation of success in combining the cited references. Applicants refer to the Stull et al. publication in an attempt to establish that the ability of aptamers to act therapeutically was unknown prior to the instant invention.

However, the examiner has made no representation regarding therapeutic efficacy of the claimed complex in combining the cited references because such efficacy is not required by the claims, which are directed to improvement of pharmacokinetic properties and targeting of therapeutic agents. The nucleic acid ligands of the instant invention are not therapeutic agents, claim 6 refers only to pharmacokinetic properties, not therapy, and claim 7 clearly recites the presence of a therapeutic agent in addition to the complex, not that the complex itself is a therapeutic agent. Therefore whether or not aptamers have drawbacks as therapeutics is irrelevant to the rejection of record.

Applicants cite the Veronese publication as providing evidence that one of skill in the art would expect a loss of activity for a nucleic acid ligand upon PEGylation and that smaller molecules cannot be "loaded" as heavily with PEG. Applicants conclude that the art does not provide an expectation of success with respect to using PEG to improve the pharmacokinetics of smaller (non-protein) drugs. This argument is not persuasive because, as noted previously, a 103 rejection does not require absolute predictability, merely a reasonable expectation of success. Because the art teaches

that conjugation of nucleic acids to compounds that increase their solubility, cellular uptake and nuclease resistance was well-known in the art prior to the time of the invention and routine synthetic methods exist for producing such complexes, there is a reasonable expectation of success in combining the cited references regardless of whether some complexes may be non-functional and routine testing may be required to determine if the three dimensional structure of an aptamer has been affected by the conjugation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
June 25, 2007